Brain tissue oxygen saturation increases during the night in adolescents

Metz, Andreas Jaakko ; Pugin, Fiona ; Huber, Reto ; Achermann, Peter ; Wolf, Martin

Abstract: How does the oxygen metabolism change during sleep? We aimed to measure the change in brain tissue oxygen saturation (StO2) before and after sleep with near-infrared spectroscopy (NIRS) using an in-house developed sensor. According to the synaptic homeostasis hypothesis [1], synaptic downscaling during sleep would result in reduced energy consumption. Thus, this reduced energy demands should be reflected in the oxygen metabolism and StO2. Thirteen nights of 7 male subjects (age 11-16 years, one subject contributed only one night, all others two) were included in the analysis. We performed NIRS measurements throughout the entire night. The NIRS sensor was placed close to electrode position Fp1 (international 10/20 system), over the left frontal cortex. Absolute StO2 and total haemoglobin (tHb) were calculated from the NIRS measurements using a self-calibrating method [2]. StO2 and tHb during the awake period prior to sleep and after awakening were compared. The subjects were instructed to lie in bed in the same position before and after sleep. Values of the two nights were averaged for each subject. Furthermore, a linear regression line was fit through the all-night StO2 recordings. We found an increase in StO2 by 4.32 ± 1.76 % (mean ± SD, paired t-test $p < 0.001$, $n = 7$) in the morning compared to evening, while tHb did not change (1.02 ± 6.81 M $p = 0.704$, $n = 7$). Since the tHb remained at a similar level after sleep, this increase in StO2 indicates that in the morning more oxygenated blood and less deoxygenated blood was present in the brain compared to the evening. The slope of the regression line was 0.37 ± 0.13 % h(-1) leading to a similar increase of StO2 in the course of sleep. This may be interpreted as a reduced oxygen consumption or energy metabolism after sleep.

DOI: https://doi.org/10.1007/978-1-4614-7411-1_16

Brain Tissue Oxygen Saturation Increases during the Night in Adolescents

A. J. Metz[a,b,d], F. Pugin[d,e], R.Huber[c,e], P. Achermann[c,f]* and M. Wolf[a,b,c]*

[a]Biomedical Optics Research Laboratory, Division of Neonatology, University Hospital Zurich, Switzerland [b]Institute for Biomedical Engineering, ETH Zurich, Switzerland [c]Zurich Center for Integrative Human Physiology, University Zurich, Switzerland [d]Member of the PhD program imMed [e]Child Development Center, University Children's Hospital Zurich, Switzerland [f]Institute for Pharmacology and Toxicology, Chronobiology and Sleep Research, University of Zurich, Switzerland, * shared last authorship

Abstract How does the oxygen metabolism change during sleep? We aimed to measure the change in brain tissue oxygen saturation (StO_2) before and after sleep with near-infrared spectroscopy (NIRS) using an in-house developed sensor. According to the synaptic homeostasis hypothesis [1] synaptic downscaling during sleep would result in reduced energy consumption. Thus, this reduced energy demands should be reflected in the oxygen metabolism and StO_2. Thirteen nights of 7 male subjects (age 11-16 years, 1 subject contributed only one night, all others two) were included in the analysis. We performed NIRS measurements throughout the entire night. The NIRS sensor was placed close to electrode position Fp1, (international 10/20 system) over the left frontal cortex. Absolute StO_2 and total haemoglobin (tHb) were calculated from the NIRS measurements using a self-calibrating method [2]. StO_2 and tHb during the awake period prior to sleep and after awakening were compared. The subjects were instructed to lie in bed in the same position before and after sleep. Values of the two nights were averaged for each subject. Furthermore, a linear regression line was fit through the all-night StO_2 recordings. We found an increase in StO_2 by 4.32 ± 1.76 % (mean ± SD, paired t-test $p < 0.001$, n=7) in the morning compared to evening, while tHb did not change (1.02 ± 6.81 μM p=0.704, n=7). Since the tHb remained at a similar level after sleep, this increase in StO_2 indicates that in the morning more oxygenated blood and less deoxygenated blood was present in the brain compared to the evening. The slope of the regression line was 0.37±0.13% h^{-1} leading to a similar increase of StO_2 in the course of sleep. This may be interpreted as a reduced oxygen consumption or energy metabolism after sleep.

1 Introduction

How does the oxygen metabolism change in the course of sleep? While different studies investigated specific events during sleep, e.g. sleep apnoea [3], differences between sleep stages [4] or wakefulness and sleep [5] the temporal evolution of

the oxygen metabolism in the course of sleep is not clear. According to the synaptic homeostasis hypothesis [1], a popular hypothesis about the function of sleep, oxygen demand should be reduced during sleep and hence brain metabolism should be decreased. A PET study [6] showed that global cerebral blood flow (CBF) after sleep was reduced compared to measurement before sleep onset. In an ultrasound doppler study in 6 healthy young males, blood flow velocity in the middle cerebral artery decreased by 6.6% between pre- and post-sleep measurements [7]. Global CBF measured with PET could be a marker for oxygen consumption [8] and in that sense the reduced global CBF may indicate a reduced energy consumption. However, this relation is not yet established and in order to obtain absolute CBF values arterial blood sampling is required. This makes PET rather impractical for sleep studies, in particular in children, which will also not be able to sleep in one position throughout the entire night. Near-infrared spectroscopy (NIRS) provides a non-invasive way to indirectly measure the oxygen metabolism which is related to the cerebral tissue oxygen saturation via the link of cytochrome C oxidase [9]. Because of its non-invasive nature and the small size of the sensor, the subjects are free to move during sleep and the discomfort is reduced to a minimum. Hence NIRS may be an interesting tool to investigate the oxygen metabolism in sleep. The aim of the current study was to investigate sleep related changes in StO_2 by comparing StO_2 before and after sleep. The synaptic homeostasis hypothesis [1] proposes a reduced energy consumption after sleep compared to before sleep, which should be reflected in StO_2.

2 Methods

Subjects: Data of seven healthy subjects (age 11-16 years, mean 13.6 years, all male) were recorded and analysed. Each subject spent two nights in the sleep laboratory at the Children's Hospital Zurich, separated by 3 weeks. Time in bed was approximately 8.5 h. Before the recordings in the sleep laboratory, the subjects had to keep a regular sleep-wake rhythm for at least 3 nights. The subjects had to fill in a sleep questionnaire and wore an activity monitor at the wrist of the non-dominant arm. This allowed us to check compliance with the instructions of keeping a regular sleep-wake rhythm. The last 3 days before the night they were not allowed to consume caffeine containing products. The study was approved by the ethical committee of the Canton of Zurich and informed consent was obtained from the legal representatives.

Protocol: The near-infrared spectroscopy (NIRS) sensor was placed at the left forehead, close to the position of electrode Fp1, international 10/20 system [10]. Additionally to the NIRS measurement, high density EEG recordings (128 electrode EEG net, Electrical Geodesics, Inc.) were performed during the night. EEG data are not presented here. In addition to the continuous measurements during the night we measured two minutes prior to light out and two minutes after

awakening. We instructed the subject to lie on his back, looking at the ceiling and not to move. With an accelerometer (ADXL330, Analog Devices) built into the sensor we were able to exclude errors resulting from wrong head positions or head movements.

NIRS measurement: NIRS measurements were performed with an in-house built NIRS device, the *OxyPrem*, which is similar to previous wireless sensors [11]. It measures light attenuation at 760nm, 805nm and 870nm, at the distances 1.5cm and 2.5cm. With this sensor we were able to calculate StO_2 for two different regions using the multi-distance method [2]. Region one is covering an area of approximately $3cm^2$ and was closer to electrode F3 (just below the hairline for most subjects). Region two was covering the same area close to electrode Fp1. Only data of region one are reported.

Post Processing: To calculate StO_2 we use the simplified diffusion constant and did not account for water in tissue, as described in assumption A4 in [12]. This approach is based on the diffusion equation for a semi-infinite medium and a point-source and implies the assumption $r(3\mu_a\mu_s')>>1$. Here r denotes the distance between source and detector, μ_a and μ_s' are the absorption and the reduced scattering coefficients, respectively.

For the scattering coefficients of the brain we used the values published by Matcher et al. [13] and thus were able to obtain total (tHb), oxygenated (O_2Hb) and deoxygenated haemoglobin (HHb). The relative change in tHb may be an indicator for the change in blood volume. The relation between StO2 and tHb is given by: $StO_2 = O_2Hb$ / tHB and $tHb = O_2Hb + HHb$. To exclude errors in StO_2 resulting from unintended movement of the subject the accelerometer data were checked. By visual inspection, only those parts were included in the analysis with values around -0.3 g and -0.7 g in the y- and z-axis of the accelerometer, respectively. In this position the subject was lying on the back. The constant g represents the earth's gravity ($\approx 9.81 ms^{-2}$). The included parts per measurement were averaged to obtain one value in StO_2 and tHb for statistical analysis. To estimate the change of StO_2 over the night we calculated a linear regression and investigate the slope (%/h; see Fig. 2). Sleep stages were visually scored according to standard criteria.

Statistics: For statistical analysis we averaged the two nights per subject, leading to 7 evening–morning StO_2 and tHb pairs. These were compared by paired t-tests. All processing was performed by Matlab® (R2009b and R2011b, The Mathworks®, Natick, Massachusetts, USA).

3 Results

We found a significant increase in StO_2 of 4.32 ± 1.76 % (mean ± SD, $p < 0.001$, n=7) in the morning compared to the evening. Mean StO_2 prior to sleep was 69.43 ± 2.02 % and 73.76 ± 2.36 % after awakening. The mean change in tHb was 1.02 ± 6.81 µM (p=0.704, n=7), which was not significant. Individual data are shown

in Fig. 1. Furthermore the O_2Hb increased by 4.27 ± 4.46 μM ($p < 0.05$, n=7) and HHb decreased by 3.25 ± 3.01 μM ($p < 0.05$, n=7).

The mean linear increase over the night was 0.37 ± 0.13 % h^{-1} (Fig. 1 and 2). The percentage increase indicates an absolute rather than a relative increase with respect to the baseline value.

4 Discussions and Conclusion

In adolescent subjects we observed an increase in StO_2 in wakefulness post sleep compared to wakefulness pre sleep. This increase was confirmed when fitting a regression line through all-night StO_2 measurements. Since tHb did not change overnight, this increase in StO_2 may indicate that in the morning more oxygenated and less deoxygenated blood was present in the brain compared to the evening. The oxygen metabolic rate can be expressed a function of CBF, arterial oxygen saturation (SaO_2) and the cerebral tissue oxygen saturation [14] and therefore our finding might be interpreted as a reduced oxygen consumption and thus energy metabolism (linked by the oxidative phosphorylation, [15], Chap. 19) after sleep. This interpretation requires SaO_2 and the CBF to be constant. Since tHb overall remains constant, the Cerebral blood volume (CBV) remains constant and hence does the CBF, which is related to the CBV [16]. Since we did not measure the SaO_2 we cannot be sure whether this assumption holds, however the subjects were healthy and no sleep apnoeas were observed during the night, which makes the assumption more plausible. A reduced energy metabolism would be in line with the synaptic homeostasis hypothesis [1], which states that synaptic downscaling during the night would lead to a reduced energy demand of the brain. Alternatively, the increased StO_2 could be linked to circadian effects (independent of sleep), as e.g. cortisol rhythm which exerts its wake promoting effect in the early morning hours [17]. As can be seen in Fig. 2 the assumed linear trend describes the StO_2 increase during sleep fairly accurate regarding the whole-night changes. But on a shorter time scale fluctuations were evident. At this point we speculate that these fluctuations are movement induced on the one hand and related to changes in sleep on the other.

In summary, in adolescents we found an increase in cerebral tissue oxygen saturation in the course of sleep, which may represent a reduced oxygen consumption of the brain and therefore a lower energy metabolism. Thus, our data are in line with the synaptic homeostasis hypothesis [1].

Acknowledgments This work was supported by the University Research Priority Program "Integrative Human Physiology", University of Zurich, Switzerland. The authors would like to thank Urs Bachofner and Madlaina Stauffer for their great support with data collection. Furthermore, Andreas Metz would like to thank Raphael Zimmermann for fruitful discussions.

References

1. Tononi G and Cirelli C (2006) Sleep function and synaptic homeostasis. Sleep Med Rev 10 (1):49-62
2. Hueber DM, Fantini S, Cerussi AE, et al. (1999) New optical probe designs for absolute (self-calibrating) NIR tissue hemoglobin measurements. Proc SPIE 3597 618-631
3. Pizza F, Biallas M, Wolf M, et al. (2010) Nocturnal cerebral hemodynamics in snorers and in patients with obstructive sleep apnea: a near-infrared spectroscopy study. Sleep 33 (2):205-10
4. Nasi T, Virtanen J, Noponen T, et al. (2011) Spontaneous hemodynamic oscillations during human sleep and sleep stage transitions characterized with near-infrared spectroscopy. PLoS ONE 6 (10):e25415
5. Spielman AJ, Zhang G, Yang CM, et al. (2000) Intracerebral hemodynamics probed by near infrared spectroscopy in the transition between wakefulness and sleep. Brain Res 866 (1-2):313-25
6. Braun AR, Balkin TJ, Wesenten NJ, et al. (1997) Regional cerebral blood flow throughout the sleep-wake cycle. An H2(15)O PET study. Brain 120 (Pt 7) 1173-97
7. Kuboyama T, Hori A, Sato T, et al. (1997) Changes in cerebral blood flow velocity in healthy young men during overnight sleep and while awake. Electroencephalogr Clin Neurophysiol 102 (2):125-31
8. Maquet P (2000) Functional neuroimaging of normal human sleep by positron emission tomography. J Sleep Res 9 (3):207-31
9. Tachtsidis I, Tisdall MM, Leung TS, et al. (2009) Relationship between brain tissue haemodynamics, oxygenation and metabolism in the healthy human adult brain during hyperoxia and hypercapnea. Adv Exp Med Biol 645 315-20
10. Jasper HH (1958) Formal discussion: dendrites. Electroencephalogr Clin Neurophysiol Suppl 35 (Supp 10):42-50
11. Muehlemann T, Haensse D and Wolf M (2008) Wireless miniaturized in-vivo near infrared imaging. Opt Express 16 (14):10323-10330
12. Metz AJ, Biallas M, Jenny C, et al. (2013) The effect of basic assumptions on the tissue oxygen saturation value of near infrared spectroscopy. Adv Exp Med Biol 765 169-75
13. Matcher SJ, Cope M and Delpy DT (1997) In vivo measurements of the wavelength dependence of tissue-scattering coefficients between 760 and 900 nm measured with time-resolved spectroscopy. Appl Opt 36 (1):386-396
14. Elwell CE, Henty JR, Leung TS, et al. (2005) Measurement of CMRO2 in neonates undergoing intensive care using near infrared spectroscopy. Adv Exp Med Biol 566 263-8
15. Nelson DL, Lehninger AL and Cox MM (2008) Lehninger Principles of Biochemistry. W H Freeman Limited, New York.

16. Grubb RL, Jr., Raichle ME, Eichling JO, et al. (1974) The effects of changes in PaCO2 on cerebral blood volume, blood flow, and vascular mean transit time. Stroke 5 (5):630-9
17. Cajochen C, Chellappa S and Schmidt C (2010) What keeps us awake? The role of clocks and hourglasses, light, and melatonin. Int Rev Neurobiol 93 57-90

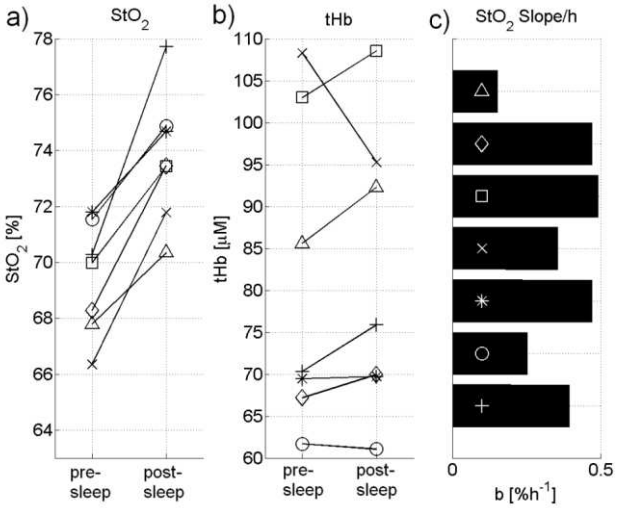

Fig. 1. a) Brain tissue oxygen saturation (StO_2) increased in the morning after sleep (post-sleep), compared to the evening before sleep (pre-sleep). The values of the two nights were averaged except for subject (+) which only contributed with one night. b) Change of total haemoglobin (tHb) from evening to morning. On average no change was observed. c) Slope of the linear regression for StO_2 for the whole night (see Fig. 2). A positive slope was observed in all subjects and all nights. The different symbols indicate the 7 subjects.

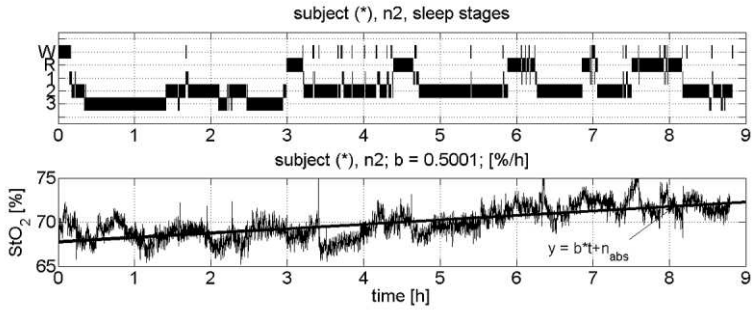

Fig. 2. Top: Visually scored sleep stages for one night of subject (*) (W: waking; R: REM sleep; 1 to 3: non-REM sleep stages N1-N3). Bottom: Corresponding time course of StO_2. A linear regression line was fitted through the data. The slope (b) of the increase during the night is indicated at the top of the panel. Please note that the b value here is given for the individual night, while the b values in Fig. 1 are averaged over two nights.